CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA
CARBOFURAN

Chemical Code # 106, Tolerance # 254
SB 950 # 127

November 3, 1987
Revised: 9/13/89, 1/22/90, 2/10/00, 7/25/00, 11/21/00, 7/17/02

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effects
Chronic toxicity, dog:	No data gap, possible adverse effects
Oncogenicity, rat:	No data gap, no adverse effects
Oncogenicity, mouse:	No data gap, no adverse effects
Reproduction, rat:	No data gap, possible adverse effects
Teratology, rat:	No data gap, no adverse effects
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, possible adverse effects
Chromosome effects:	No data gap, no adverse effects
DNA damage:	No data gap, no adverse effects
Neurotoxicity:	Not required at this time*

*Acceptable developmental and subchronic neurotoxicity studies have been reviewed.

Toxicology one-liners are attached.
All relevant record numbers through 178009 (Document No. 254-170) have been examined. This includes all records on file as of 11/21/00.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T020717.doc
Revised by C. Aldous, 2/10/00; M. Silva, 7/25/00, 11/21/00 & 7/17/02

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED (CHRONIC AND ONCOGENICITY), RAT

096-098 047717-19, "Two-Year Dietary Toxicity and Carcinogenicity Study in Rats - Carbofuran Technical", (IRDC, 12/18/79, report no. 167-115). Carbofuran technical, MrS1314, 95.6% AI; 100, 20, 10, or 0 ppm in the feed to 90/sex/level with interim sacrifices of 10/sex/level at 6, 12, 18 months (total 60/sex/level for 2 years). No adverse effect.** NOEL [excluding cholinesterase (ChE) inhibitional] = 20 ppm (> 10% body weight decrement in males throughout most of study duration, lesser decrement in female body weight. ChE inhibition NOEL = 20 ppm (minor but consistent plasma, RBC, and brain ChE inhibition in both sexes at 100 ppm). Report complete. Acceptable**.** (F Martz/C Aldous, 10/30/87. EPA Guideline: Oncogenic NOEL = 100 ppm (HDT); Systemic NOEL = 20 ppm; ChE NOEL = 20 ppm.

029 038431, Summary of above and included with report.

044 007654, Duplicate of above.

048 007671 A reference to submitting a study (047717) to EPA.

030 022790 Brief summary of a 2-year rat chronic study on carbofuran administered at 1, 10, 25, 50 and 100 ppm.

001-002 022784/022785, 022858 Summaries similar to 022790.

CHRONIC TOXICITY, DOG

Subchronic Studies:

169 175910 "14-Day Oral Toxicity (Range Finding) Study in Beagle Dogs of Carbofuran," (Burtner, B.R.; Toxigenics, Incorporated, Decatur, Il; Study #: 410-0714; 1/5/82). Carbofuran technical (96.1% pure) was fed in diet to Beagle dogs (1/sex/dose) at 0, 18, 32, 56, 100 and 316 ppm for 14 days. The dogs treated at 18 ppm had their dose increased to 1000 ppm from day 4 to 14 (11 days). The increased dose (1000 ppm) was meant to demonstrate an effect in RBC cholinesterase activity. At the end of the 14 day treatment, dogs were retained on a maintenance diet for an additional 29 days. The test was a total of 43 days. Systemic NOEL = 100 ppm (There was decreased food consumption and increased bodyweight loss in both sexes at 1000 ppm. Bodyweight and food consumption was also decreased at 316 ppm (first week of treatment & male food intake at day 14). This effect at 316 ppm was transitional in both sexes. At 1000 ppm, dogs showed muscle tremors, emesis (nonformed) and salivation (male only). ChE NOEL = 18 ppm (Plasma ChE was decreased at $\geq$ 32 ppm.) RBC ChE was not inhibited at any dose and brain ChE was not measured. No adverse effect indicated. These data are supplemental. M. Silva, 7/19/00.

166 175907 "4-Week Oral Toxicity (Feeding) Study With Carbofuran (D 1221) in Male Dogs," (Bloch, I., Frei, Th., Luetkemeier, H., Vogel, W., Terrier, Ch.; RCC, AG & RCC Umweltchemie AG, Itingen, Switzerland; RCC Project #: 087963; 9/14/87). Carbofuran technical (99.6% pure) was fed in diet to male Beagle dogs (4/dose) at 0 and 5 ppm (approximately 0.22 mg/kg) for 4 weeks. There was an increase in clinical signs (vomiting and mucus in feces; 4/4 versus 2/4 controls) and a decrease in erythrocyte cholinesterase activity at 5 ppm.) At 5 ppm, there was a minimal decrease

in ERY-ChE in males. The pretest value for ERY-ChE was statistically significantly lower at 5 ppm, compared to controls. No adverse effect indicated. These data are supplemental. M. Silva 7/19/00.

** 165 175906 "13-Week Oral Toxicity (Feeding) Study With Carbofuran (D1221) in the Dog," (Bloch, I., Frei, Th., Madoerin, K., Luetkemeier, H., Vogel, W., Schlotke, B., Vogel, O., Terrier, Ch.; RCC Research & Consulting Co., AG & RCC Umweltchemie AG, Itingen, Switzerland; RCC Project #: 077837; 12/4/87). Carbofuran technical (99.6% pure) was fed in diet to Beagle dogs (4/sex/dose—necropsy after 13 weeks of treatment; 2/sex/dose—necropsy after 13 weeks of treatment + 4 weeks of recovery) at 0, 10, 70 and 500/250 ppm. NOEL = 10 ppm; approximately 0.43 mg/kg/day (One dog (38F), treated at 500 ppm, died on day 5. There was an increase in hyperemia of the ear pinnae (foci or larger areas), abdominal skin and oral mucous membranes and an increase in salivation (most frequent at $\geq$ 70 ppm). Only high dose dogs showed muscle spasms (twitching of the fascial muscles occasionally accompanied by tremors), ataxia, decreased motility, tachypnea, deep respiration and vomiting. Bodyweights and food consumption were significantly decreased at 500 ppm, with some recovery after the dose was lowered. Plasma and erythrocyte ChE were inhibited at $\geq$ 70 ppm.) No adverse effect. Acceptable. M. Silva 7/19/00.

Chronic Studies:

****099-103 047720-24**, "One-Year Chronic Oral Toxicity Study in Beagle Dogs with Carbofuran", (Toxigenics, 6/6/83). Carbofuran technical, 96.1% pure; 500, 20, 10, or 0 ppm AI in the diet to 6/sex/level for 1 year; **Adverse effects:** At 500 ppm weight loss and inanition due to food emesis and loose stools, erythroid parameter decrease and electrolyte changes, males>females, moderate inflammatory lung changes, kidney weight increase and heart weight decrease, thyroid weight decrease in males, testicular degeneration and weight decrease; At 20 ppm: testes weight decrease; Brain weight reduction in all treated male groups, no NOEL, brain histopathology normal. Report complete and acceptable. (F. Martz, 12/8/86).
EPA 1-liner: Minimum; NOEL = 20 ppm (mid-dose) = 0.5 mg/kg day; AChE depression (plasma and RBC) and seminiferous tubule degeneration, giant cell formation in testes, aspermia; uterine hyperplasia and hydrometria.

044 007652, Summary of 047720-24.

030 022791, A brief summary of a 2-year chronic study on carbofuran administered to beagles.

001-002 022782/022857, Summaries similar to 022791.

ONCOGENICITY, MOUSE

****104-08 047725-29, "2-Year Dietary Toxicity and Carcinogenicity Study in Mice", (IRDC, 1/4/80). Carbofuran technical, 95.6% Ai; 500, 125, 20, or 0 ppm in the feed to 100/sex/level CD-1 mice with interim sacrifice of 10/sex/level at 6, 12, and 18 months; No adverse effect, no meaningful effects; toxic/oncogenic NOEL>500ppm; brain cholinesterase inhibition NOEL=20 ppm. Initially reviewed by F. Martz (12/11/86) as unacceptable (no MTD). After review of the supplemental dose justification provided in records no. 065475 and 087709, the study is upgraded to "acceptable". G. Chernoff, 1/22/90.
EPA Guideline: oncogenic NOEL = >500 ppm (HDT); Systemic NOEL = 125 ppm; ChE NOEL = 20 ppm.

130 065475, Supplement to record # 047725-29, containing information for justification of selected dosing levels.

136 087709, "Acute dietary pilot study of carbofuran in mice", (Bio/dynamics Inc., Study # ACT 128.22, 9/21/78). Supplement to record 047725-29, consisting of the study used for dose justification.

029 939872, Summary of record # 047725-29.

044 007655; 048 007664, Duplicates of 939872.

030 022788, Brief summary of an oncogenicity study on carbofuran administered at 30 or 100 ppm to mice.

REPRODUCTION, RAT

****091-93 047712-14**, "Three Generation Reproduction Study in Rats", ((CD) IRDC, 11/9/79). Carbofuran technical grade, 95.6% pure, in the feed at 100, 20, or 0 ppm. Possible adverse effects: reduced body weight gain of adults and reduced birth weights of offspring with decrement worsening to 15% by weaning, NOEL=20 ppm; no meaningful organ weight or microscopic changes in adults or offspring. Complete and acceptable**.** (F. Martz, 12/23/86).
EPA 1-liner: Minimum; NOEL = 20 ppm; Levels tested = 0, 20 and 100 ppm.

048 007672, In reference to submitting a study (047712-14) to EPA.

029 939877, Summary of 047712-14.

044 007653, 048 007663, Duplicates of 939877.

030 022786, A brief summary on a reproduction study with carbofuran administered at 10 and 50 ppm to rats for one year.

001 022780, Summary similar to 022786.

001 022781, Brief summary of a 3-generation rat reproduction study on carbofuran administered at 1, 10, 30 and 100 ppm.

030 022789, Brief summaries of 022786 and 022781.

[no DPR Record No.] Pant, N., A. K. Prasad, S. C. Srivastava, R. Shankar, and S. P. Srivastava, “Effect of oral administration of carbofuran on male reproductive system of rat”, published in *Human & Experimental Toxicology* **14:**889-894 (1995). Male Druckrey rats were dosed with technical carbofuran (97.2% purity) by gavage (peanut oil vehicle) at 0, 0.1, 0.2, 0.4, or 0.8 mg/kg/day (10/group), 5 days/wk for 60 days. At sacrifice, reproductive structures were weighed, testes were taken for histopathology and testicular enzyme assays, and epididymal sperm were evaluated for motility, count, and abnormalities. Seven of the 10 high dose rats died survivors showed lethargy and imbalance. Other groups did not show clinical signs. Progressive body weight decrements occurred at 0.2 mg/kg/day and above. Weights of epididymides, seminal vesicles, ventral prostate, and coagulating glands were significantly reduced at 0.2 mg/kg/day and above. Sperm motility and sperm counts were reduced at these dose levels. Increased numbers of sperm necks and tails were bent or curved, or tails were otherwise misshapen at the same dose levels. Testicular enzyme levels were altered at 0.2 mg/kg/day and above: reduced glucose-6-phosphate dehydrogenase and sorbitol dehydrogenase were considered to reflect disturbed germ cell maturation, whereas elevated

γ-glutamyl transpeptidase and lactate dehydrogenase levels were taken to indicate alterations in Sertoli cells and germinal epithelium, respectively. Histopathology of testes at 0.2 mg/kg/day and above included moderate edema and congestion among seminiferous tubules. There was moderate vacuolization of Sertoli cells and germinal cells at and above 0.2 mg/kg/day, with no change in Leydig cell appearance. Progressively higher dose levels led to tubular atrophy, disturbed spermatogenesis, and in some cases, atrophy of affected cell types. Supplemental data, useful but not relevant to U. S. EPA data requirements. Damage to reproductive tissues constitutes a "possible adverse effect". Aldous, 11/17/99.

[no DPR Record Number] Pant, N., R. Shankar, and S. P. Srivastava, "*In utero* and lactational exposure of carbofuran to rats: effect on testes and sperm", published in *Human & Experimental Toxicology* **16:**267-272 (1997). Druckrey female rats of proven fertility were dosed with technical carbofuran (97.2% purity) by gavage (peanut oil vehicle) as follows: 6/group were dosed with either 0 or 0.4 mg/kg/day carbofuran daily throughout pregnancy, or 4/group were dosed with 0, 0.2 or 0.4 mg/kg/day carbofuran daily during lactation days 0 to 21. In all instances, pups were weaned at day 21, and 5/litter were examined at day 90 p.c. for epididymal sperm appearance and motility, activities of key testicular enzymes, sperm motility, sperm count, and sperm abnormalities. At 0.4 mg/kg/day in gestation and lactation treatment groups, there were reductions in sorbitol dehydrogenase, and increases in lactate dehydrogenase and γ-glutamyl transpeptidase. Also, at 0.4 mg/kg/day after gestation or lactation treatment, epididymal sperm evaluations showed decreased sperm motility, decreased sperm count, and increased sperm abnormalities. Histopathology was most strongly evident after *in utero* exposure: individual seminiferous tubules lacked spermatogenic activity and Sertoli cells were frequently degenerated. There were no effects at 0.2 mg/kg/day. The consistency and magnitude of the changes at 0.4 mg/kg/day indicate "possible adverse effects." Supplemental study. Aldous, 11/17/99.

REPRODUCTION, OTHER SPECIES

113 050382, "Reproduction Study with NIA 10242 Technical (Furadan) in Beagle Dogs". IBT dog reproduction study, validation "pending"; no effects noted at 20 or 50 ppm via the feed. (F. Martz, 12/15/86).

030 022787, Brief summary on a one-year dog reproduction study with carbofuran administered at 20 and 50 ppm.

001 022822/022812, Summaries similar to 022787.

TERATOLOGY, RAT

** 254 - 094, 130 & 138 047715, 065475 & 087711 "Teratology Study in the Rat with Carbofuran," (Rodwell, D.E.; IRDC, Mattawan, MI;12/26/80). Carbofuran technical (95.6% pure) was administered by gavage to Charles River COBS® CD® (25/dose) at 0 (corn oil), 0.25, 0.5 and 1.2 mg/kg/day on gestation days 6-15 (copulation = day 0). Maternal NOEL = 0.5 mg/kg (The only treatment-related effect was a very slight and transitional decrease in maternal weight gain during gd 6 - 12 (30 - 50% decrease). Developmental NOEL > 1.2 mg/kg (There were no treatment-related effects at any dose (no malformations, variations or fetotoxicity).) Initially reviewed by FM (12/11/86) as unacceptable (no MTD), but possibly upgradeable with a dose justification. After review of supplemental information (DPR volume/record #s: 130/065475 & 138/087711) the study is upgraded to acceptable (Kishiyama, Chernoff, 9/13/89). Re-reviewed by Silva, 7/8/02
EPA 1-liner: Minimum; Teratogenic NOEL≥ 1.2 mg/kg/ (HDT); Fetotoxic NOEL = 1.2 mg/kg (HDT); Levels tested = 0, 0.25, 0.5 & 1.20 mg/kg.

138 087711 "Teratogenicity of Carbofuran in Rats," (Rao, G.N.; Warf Institute, Incorporated, Madison, WI; Warf Institute Code #: T-730; 7/21/78). Carbofuran technical (95.6% pure) was administered by gavage to mated Sprague-Dawley CD rats (24/dose) at 0 (0.25% methyl cellulose), 0.1, 0.3 and 1.0 mg/kg/day on gestation days 6-15 (copulation = day 0). Maternal NOEL = 0.1 mg/kg (Clinical signs occurred at $\geq$ 0.3 mg/kg/day (death at 1.0 mg/kg.)) Developmental NOEL = 1.0 mg/kg (No treatment-related effects occurred at any dose.) The findings in this study rat teratology study provide a clear rationale for the dose selection used in the definitive study. Based on dose-rangefinding results, as well as a lack of developmental effects, the status of the definitive rat developmental study is upgraded to acceptable (no adverse effects indicated). M. Silva, 6/22/00.

029 939875, Summary of 047715. (J. Wong, 5/28/85)

130 065475, Supplement to 047715 containing information on the justification used in selecting dose levels.

113 050381, "Teratology and Postnatal Study in the Rat with Carbofuran", ((CD) IRDC, 1/8/81). Carbofuran technical, 95.6% pure, in the feed at 160, 60, 20, 0 ppm to 40/level during gestation days 6-19 (plug day=0); 20 gravid/level sacrificed on day 20, remainder allowed to deliver and nurse to weaning; Maternal body weight loss/reduced gain and anorexia, NOEL=20 ppm; No malformations/variations,** teratogenic NOEL>160 ppm (11 mg/kg/day); neonatal weight decrease and growth retardation, NOEL=60 ppm (4.4 mg/kg/day). Report complete and "acceptable". (F. Martz, 12/15/86).
EPA 1-liner: Minimum; Teratogenic NOEL $\geq$ 160 ppm (HDT); Fetotoxic NOEL = 20 ppm reduced body weight.

029 939873, Brief summary of pilot study for 050381; IRDC, no date; 200, 160, 120, 60, 20, or 0 ppm in the feed; dose-related initial weight loss, NOEL=20 ppm; no other effects reported. Top dose level of 160 ppm chosen from body weight effects. (F. Martz, 12/22/86).

029 939874, Summary of 050381.

No volume or record #s. "Hazardous Effects of Carbofuran on Pregnancy Outcome of Rats," (Jayatunga, Y.N.A., Dangalle, C.D. and Ratnasooriya, W.D.; Department of Zoology, University of Colombo, Colombo, Sri Lanka; submitted 11/18/97: Medical Science Research, ***26***:33 - 37, 1998). "Unformulated" carbofuran (purity not specified) was administered to pregnant adult Wistar rats (6/dose) at 0 (corn oil), 0.2, 0.4 and 0.8 mg/kg consecutively on gestation days (gd) 1 through 5. On gd day 5, rats were scored for head dips, rears and locomotor activity. Two to 3 hours before treatment and on gd day 5, resistance offered by each rat was assessed. On gd 14, animals were laporatomized under ether and the fetuses were examined. Subsequently, rats were sutured and received local and subcutaneous antibiotics (polymycine) and were allowed to recover and deliver. Ovariectomized rats were treated for 5 consecutive days at 0 and 0.4 mg/kg carbofuran and were assessed for estrogenic and antiestrogenic activities (8 rats/dose/test). Antiprogesterone activity (6 rats/dose) of carbofuran was tested at 0 and 0.4 mg/kg in pregnant rats during gd 1 – 5. A separate LD_{50} experiment was performed (12 rats total, no doses provided; summary only). Maternal NOEL < 0.2 mg/kg (There was increased estrogenicity at 0.4 mg/kg, decreased body weight gain, food and water consumption at $\geq$ 0.4 mg/kg, increased pre-implantation loss and gestation length at $\geq$ 0.4 mg/kg, as well as increased bradycardia, hematology effects and sedative/cholinergic effects at $\geq$ 0.2 mg/kg.) Developmental NOEL = 0.2 mg/kg (there was a statistically significant increase in cranial length of pup, length of pup body, gain in pup body weight, time for fur to appear, decreased

fetal survival ratio (%) and time taken to open eyes at ≥ 0.4 mg/kg.) Currently, it is not possible to conclude whether or not there is an adverse effect. M. Silva, 7/15/02

No volume or record #s. "Effects of Mid-Term Exposure to Carbofuran on Pregnancy Outcome of Rats," (Jayatunga, Y.N.A., Dangalle, C.D. and Ratnasooriya, W.D.; Department of Zoology, University of Colombo, Colombo, Sri Lanka; submitted 6/27/97: Medical Science Research, ***26***:679 - 683, 1998). "Unformulated" carbofuran (purity not specified) was administered to pregnant adult Wistar rats (6/dose) at 0 (corn oil), 0.2, 0.4 and 0.8 mg/kg consecutively on gestation days (gd) 8 through 12. On gd 17 animals were laporatomized under ether and the fetuses were examined. Subsequently, rats were sutured and received local and subcutaneous antibiotics (polymycine) and were allowed to recover and deliver. Maternal NOEL < 0.2 mg/kg (Transient, overt clinical signs of cholinergic toxicity occurred (excess salivation, lachrymation, pupil constriction, production of soft feces, almost colorless urine). Mild to moderate adrenergic (piloerection without exophthalmia) toxicity followed dosing. Mild vaginal bleeding occurred in 3/6 rats at 0.4 mg/kg on gd 11 (day 4 of treatment). This effect lasted for 2 days. There was a significant linear correlation between the doses of carbofuran tested and the inhibition in locomotor activity (r^2 = -0.47; $p < 0.05$) and number of head dips (r^2 = -0.64; $p < 0.01$). Developmental NOEL cannot be determined since there were no consistent dose-related effects. Currently, it is not possible to conclude whether or not there is specifically an adverse developmental effect. M. Silva, 7/15/02

TERATOLOGY, RABBIT

**095 047716, "Teratology Study in the Rabbit with Carbofuran", ((NWZ) IRDC, 4/20/81). Carbofuran technical, 95.6%, in aqueous Methocel at 2.0, 0.5, 0.12, or 0 mg/kg/day by oral gavage on gestation days 6-18 (insemination = day 0), 20/group; No adverse effects; no malformations, variations, fetotoxicity, or maternal toxicity at any level; very slight, toxicologically insignificant reduction of maternal weight gain at 2.0 mg/kg/; NOEL>2.0 mg/kg/day. Initially reviewed by F. Martz (12/11/86) as unacceptable (no MTD or analysis of dosing suspension), but possibly upgradeable. After review of supplemental dosing suspension data (record #065475), and dose justification study (record #087710), the study is upgraded to "acceptable". G. Chernoff, 1/22/90.
EPA 1-liner: Minimum; Teratogenic NOEL>2.0 mg/kg/day HDT; Fetotoxic NOEL> 2.00 mg/kg/day HDT.

130 065475, Supplement to record #047716, containing information on the selection of dose levels and solution preparation.

137 087710, "Teratology study of Carbofuran in rabbits", (WARF Institute, Inc., study # Act 185-33, 6/24/78). Supplemental to record no. 047716, consisting of the study used to justify subsequent dose selections.

029 939876, Summary of study in record #047716.

048 007665, Brief summary (statement) on 047716.

030 022792, Brief summary of a rabbit teratology study on carbofuran administered at 2.0, 0.5, 0.12 and 0 mg/kg/day.

GENE MUTATION

SUMMARY: The test article is a weak mutagen in Ames test and in mouse lymphoma systems, but not mutagenic in Drosophila at tolerated dose levels. The gene mutation data requirement is filled with a **possible adverse effect** found in both microbial and mammalian systems in vitro. Since carbofuran is an insecticide, Drosophila are not a good test system because of lethality. Although two of the studies in Drosophila were conducted according to guidelines, the negative results are of questionable biological significance for possible effects in mammals (Martz and Gee, 11/87).

BACTERIA

110 047749, "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides (carbofuran): Reverse Mutation in Salmonella typhimurium and Escherichia coli." (SRI, 1979). Carbofuran, no purity stated, lot No. C-4717-54A; strains TA 1535, TA 1537, TA 1538, TA98, TA100, also, E. coli WP2 uv A; ± S9, single plate each concentration, two trials at 0, 1, 10, 50, 500, 1,000 5,000 µg/plate; no evidence for increase in reversion rate. **Unacceptable** (missing info.). (J. Gee, 12/11/86).

109 047731, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (Microbiological Associates, 9/22/83). Carbofuran, Lot RHB-09/10-0112, no purity stated; tested with and without S9 from rat liver at 0, 100, 500, 2,500, 5,000 and 10,000 µg/plate in triplicate, one trial. Strains TA 1535, TA 1537, TA 1538, TA98, and TA 100. **Possible adverse effect:** weak positive response in TA1535 - S9 but not in others. **Unacceptable:** not independently upgradeable**:** single trial, no purity given. (J. Gee, 12/10/86).

109 047732, "Salmonella/Mammalian-Microsome Incorporation (Ames Test)", (Microbiological Associates, 1983). Carbofuran, lot No. RHB-11-0202, no purity given; strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100, tested in triplicate at 0, 100, 500, 2,500, 5,000 or 10,000 µg/plate ± rat liver activation, single trial; **Possible adverse effect:** marginal (>2- fold) increase in revertants/plate in TA 1535, no activation; **Unacceptable**, not upgradeable**:** (single trial, no purity given). (J. Gee, 12/10/86).

109 047733, "Salmonella/Mammalian Microsome Plate Incorporation Point Mutation Assay (Ames Test)", (Microbiological Associates, 1983). Carbofuran, lot # E 2700-112D, no purity stated; strains TA 1535, TA 1537, TA 1538, TA 98, TA 100 ± rat liver activation, tested + S9 at 0, 100, 500, 2,500, 5,000 or 10,000 µg/plate, -S9 at 0, 50, 250, 1,250, 2,500 or 5,000 µg/plate, in triplicate, single trial. **Possible adverse effect:** weak positive response in TA1535 - S9 but not in others. **Unacceptable**, not independently upgradeable. (single trial, no purity given). (J. Gee, 12/10/86).

109 047734, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)". (Microbiological Associates, 1983). Carbofuran, lot No. 2700-112E, no purity stated; strains TA 1535, TA 1537, TA 1538, TA 100, and TA 98 tested ± rat liver S9 at 0, 100, 500, 2,500, 5,000, or 10,000 µg/plate in triplicate, single trial; **Possible adverse effect**: marginal (<2-fold) increase in reversion in TA 1535, -S9. **Unacceptable**, not independently upgradeable. (single trial, no purity). (J. Gee, 12/10/86).

109 047735, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (Microbiological Assoc., 1983). Carbofuran, Lot E2700-114A, no purity states; strains TA 1535, TA 98, TA 100 ± rat liver activation; tested at 0, 100, 500, 2,500, 5,000, or 10,000 µg/plate in triplicate, single trial. **Possible adverse effect:** marginal increase in revertants in TA 1535, -S9

only; **Unacceptable**, not independently upgradeable (single trial, no purity stated). (J. Gee, 12/10/86).

109 047736, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (Microbiological Assoc., 1983). Carbofuran, Lot E2700-116A, no purity stated; tested with strains TA 1535, TA 1537, TA 1538, TA 98 or TA 100 ± from rat liver at 0, 100, 500, 2,500, 5,000 or 10,000 µg/plate in triplicate, single trial, **Possible adverse effect:** 1.9-fold increase with conc. in TA 1535, -S9, not in other strains. **Unacceptable**, not independently upgradeable (single trial, no purity given). (J. Gee, 12/10/86).

109 047737, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (Microbiological Assoc., 1983). Carbofuran, Lot No. E2700-154A, no purity stated; strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 ± rat liver activation at 0, 100, 500, 2,500, 5,000 or 10,000 µg/plate, in triplicate, one trial. **Possible adverse effect:** 1,8-fold increase with TA 1535 and 1.4-fold increase in TA 100 revertant without activation. **Unacceptable**, not independently upgradeable (single trial, no composition of test article). (J. Gee, 12/10/86).

109 047738, "Mutagenicity Evaluation of FMC 10242 (Carbofuran) in the Ames Salmonella/Microsome Plate Test, Final Report", (Litton Bionetics, 1983). Carbofuran, Lot E2700-154A; 97.6% strains TA 1535, TA 1537, TA 1538, TA 98 or TA 100 ± rat liver activation at 0, 1, 10, 100, 500, 1,00, 2,500, 5,000 or 10,000, µg/plate in triplicate, single trial. Negative for mutagenicity. **Unacceptable**, not independently upgradeable (single trial). (J. Gee, 12/10/86).

109 047739, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (Microbiological Assoc., 1983). Carbofuran, Lot No. E2915-100A, no purity stated; strains TA 1537, TA 1538, TA 98 and TA 100 ± rat liver S9 at 0, 100, 500, 2,500, 5,000, or 10,000 µg/plate in triplicate, single trial; **Possible adverse effect:** marginally increased incidence of revertants in TA 1535 and TA 100. **Unacceptable**, not independently upgradeable (no repeat trial). (J. Gee, 12/10/86).

MAMMALIAN CELLS

****109 047740**, "L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay", (Microbiological Assoc., 1983). Carbofuran, 98% Lot 2700-154A, ± rat liver activation at 0 to 211 µg/ml - S9 for 4 hours; **Possible adverse effect:** increased mutation frequency with conc. in -S9 series. **Acceptable.** (J. Gee, 12/10/86).

109 047741, "L5178 TK+/- Mouse Lymphoma Mutagenesis Assay", (Microbiological Assoc., 1983). Carbofuran technical, lot E2915-100A; no purity stated; ± S9 at 0 to 316 µg/ml -S9, 0 to 1780 µg/ml +S9, 4 hours incubation; single trial. **Possible adverse effect:** concentration - dependent increase in mutation frequency. **Unacceptable**, not independently upgradeable (no purity of test article, single trial). (J. Gee 12/11/86).

DROSOPHILA

****109 047742**, "Drosophila Sex-Linked Recessive Lethal Assay of 2,3-dihydro-2,2-dimethyl-7-benzofuranyl N-methyl Carbamate (Carbofuran)", (U. of Wisconsin, 1983). Carbofuran, 98%, Lot E2700-154A, tested at 0 or 7.5 ppm (17% mortality), 22 hours by feeding; 10% ethanol - 5% sucrose; no evidence of sex-linked recessive lethal effect. **Acceptable**

(acknowledging limitations due to high toxicity of an insecticide on an insect as test organism). (J. Gee, 12/11/86).

109 047743, "Mutagenesis Screening (sex-linked recessive) of Pesticides Using Drosophila", (WARF Inst., 1981). Carbofuran, no lot number or purity; fed (+ contact) to Canton-S males (number not given) at 0 or 10 ppm , 24 hours; mated 4, 3, 3, 4, days to females (numbers not included); high mortality; no apparent adverse effect: no evidence of sex-linked recessive lethal effect. **Unacceptable** (missing data). (J. Gee, 12/11/86).

109 047744, "Mutagenicity Evaluation of FMC 10242 (Carbofuran) for the Sex-Linked Recessive Lethal Test in Drosophila melanogaster, Final Report", (Litton Bionetics, 1983). Carbofuran, 97.6%, lot No. RHB-11; fed to > 200 males at 0, 5, 10 µg/ml, 24 hours, mated 1:3 to produce 2 broods (1-3, 4-7 days); no evidence of SLRL effect. **Acceptable. (J. Gee, 12/11/86).

CHROMOSOME EFFECTS

in vitro

110 047747, "Chromosome Aberration Assay of FMC 10242 (Carbofuran) in Chinese Hamster Ovary (CHO) Cells". (Microbiological Assoc., 183). Carbofuran, (2 hours), 98% Lot No. E2700-154A; tested +S9 at 0, 312.5, 625, 1250 or 2500 µg/ml; -S9 at 0, 2.5, 10, 50 or 100 µg/ml 16-19 hours; duplicate cultures, scored 50 cells per culture. No apparent adverse effect; no evidence for cytogenetic effects stated to be out historical range. **Unacceptable**, upgradeable (need historical range, other specific questions in CDFA review). (J. Gee, 12/11/86).

110 047748, "Chromosome Aberration Assay of FMC 10242 (Carbofuran) in Chinese Hamster Ovary (CHO) Cells." (Microbiological Assoc., 1983). Carbofuran technical 96%; Lot E2915-100A; CHO cells tested +S9 at 0, 312, 625, 1,250 or 2,500 µg/ml, 2 hours; -S9 at 0, 50, 100, 500, or 1,000 µg/ml, 14 hours. Scored 50/flask, duplicate flasks. No apparent adverse effect: indicated no increase in aberrations reported but needs historical control range to confirm. **Unacceptable**, upgradeable (see review**).** (J. Gee, 12/11/86).

110 047755, "Sister Chromatid Exchange Assay of FMC 10242 (Carbofuran) in Chinese Hamster Ovary Cells", (Microbiological Assoc., 1983). Carbofuran, Lot E2915-100A, [purity 96%: see 110:47748]; CHO ± rat liver S9; +S9, 2 hours at 0, 78, 156, 312, 625, 1,250, or 2,500 µg/ml; or -S9, 24 hours at 0, 6.25, 12.5, 12.5, 25, 50, 100, or 200 µg/ml. No apparent adverse effect (no evidence for increase in sister chromatid exchanges). **Acceptable. (J. Gee, 12/12/86).

110 047754, "Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells", (Microbiological Assoc., 1983). Carbofuran, Lot E2700-154A [98%]; CHO cells ± rat liver activation at 0, 78, 156, 312, 625, 1,250 or 2,500 µg/ml, incubated 2 hours +S9 (scored lowest 3 due to cytotoxicity at highest 3 treatment levels): Incubated at 0, 6.25, 12.5, 25, 50, 100, or 200, µg/ml for 24 hours -S9. No apparent adverse effect (no increase in sister chromatid exchanges). **Acceptable. (J. Gee, 12/12/86).

in vivo

109 047745, "Activity of FMC 10242 (Carbofuran) in the In Vivo Cytogenetics Assay in Sprague-Dawley rats, Final Report". (Microbiological Assoc., 1983). Carbofuran, 98% technical, Lot 2700-154A; 5 males (rats) per group were dosed in 5 consecutive days at 0, 0.6, 2.0 or 6.0 mg/kg by

oral gavage and sacrificed at 6 hours after the last dose. No adverse effect was reported. **Unacceptable** (males only, single sacrifice time). (J. Gee, 12/11/86).

109 047746, "Activity of FMC 10242 (Carbofuran) in the Subchronic In Vivo Cytogenetics Assay in Male Rats, Final Report". (Microbiological Assoc., 1983). Carbofuran, 96%; Lot No. E2915-100A; given by oral gavage to S-D male rats at 0, 1, 6 or 10 mg/kg/day for 5 days, sacrificed 6 hours after last dosing, scored 50 metaphases/animal. No apparent adverse effect, **Unacceptable** (males only, single sampling time), no deaths. (J. Gee, 12/11/86).

029 939879, One-page summary report on a dominant-lethal mutagenicity study. An audited IBT study... carbofuran administered with a single intraperitoneal injection at 0, 0.25 and 0.5 mg/kg.

048 007673, Report similar to 939879.

030 022793, Brief summaries of 007673/939879.

001 022784, Report similar to 939879 and 007673.

030 022790, Partial summaries of 022784/939879/007673.

DNA DAMAGE

BACTERIA

110 047751, "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides (Carbofuran): DNA Damage and Repair with Escherichia coli and Bacillus subtilis", (SRI, 1979). Carbofuran, no purity stated, Lot No. C04717-54A; no activation, 1 plate per concentration, 1 trial. E. coli W3110 and p 3478; B. subtilis H17, M45 at 0, 0.01, 0.10, 1.0 or 5.0 mg per 6 mm disk. No apparent adverse effect. **Unacceptable,** not upgradeable (no activation, inadequate concentration range: no cytotoxicity). (J. Gee, 12/12/86).

MAMMALIAN CELL CULTURES

110 047750, "Unscheduled DNA Synthesis in Rat Primary hepatocytes." (Microbiological Assoc., 1983). Carbofuran; Lot E2700-154A, 98%; primary rat hepatocytes; tested at 0, 1, 5, 10, 50 or 100 µg/ml, 18 hours; autoradiography, 75 cells scored per concentration; No evidence of UDS. Acceptable.** (J. Gee, 12/12/86).

110 047753, "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides: Unscheduled DNA Synthesis in Human Fibroblasts", (SRI, 1979). Carbofuran, no purity stated Lot -c4717-54A; W1-38 unscheduled DNA synthesis ± S9 (rat liver), DPM/µg isolated DNA, at 0, 0.1, 1.0, 10, 100 or 1,000 (ppt) µg/ml 1 hour + S9, 3 hours -S9, No evidence of UDS. **Unacceptable,** possibly upgradeable (see review). (J. Gee, 12/12/86).

YEAST

110 047752; 844, "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides: Mitotic Recombination in Saccharomyces cerevisiae", (SRI, 1979), Carbofuran, no purity stated; Lot No. C-4717-54A; ± rat liver S9 at 0, 0.1, 0.5 1.0 or 5.0 % w/v, Trial 1; 0, 1, 2, 4, or 5 % w/v, trial 2; 4 hours exposure; No apparent adverse effect**:** no concentration-related increase; **Unacceptable** (missing data). (J. Gee, 12/12/86).

029 939878, Brief summary of in-vitro microbiological mutagenicity and unscheduled DNA synthesis studies (047749, 047751, 047752, 047753).

029 046696; 044 007651; Duplicates of 939878.

NEUROTOXICITY

** 170 178009 "Carbofuran Technical Subchronic Neurotoxicity Screen in Rats," (Freeman, C.; FMC Corporation, Toxicology Laboratory, Princeton, NJ; Study #: A92-3705; 2/25/94). Carbofuran technical (99.5% pure) was fed in diet to Charles River Sprague-Dawley CD rats (10/sex/dose) at 0, 50, 500 and 1000 ppm for 13 weeks. FOB and motor activity testing was done at pretest and after the 4th, 8th and 13th week of treatment. Systemic NOEL = 50 ppm (Food consumption in both sexes was intermittently decreased at 1000 ppm. Gait impairment was the primary effect at $\geq$ 500 ppm in both sexes (staggered gait, splayed hindlimbs, ataxia, exaggerated hindlimb flexion) and a reduced hindlimb grip strength. Females at $\geq$ 500 ppm had exopthalmos and at 1000 ppm, females had an increased number of urine pools. Females at 1000 ppm showed decreased motor activity following the 4th and 8th weeks of treatment.) Neurohistopathology NOEL > 1000 ppm (There were no neuropathologic effects at any dose that were treatment-related.) No adverse effect. Acceptable. (M. Silva, 11/20/00)

SPECIALIZED STUDIES COMPLETED

**254-153 138360 Ponnock, K. S., "A developmental neurotoxicity study of carbofuran in the rat via dietary administration" Pharmaco LSR, Inc. 8/30/94. FMC Study # A93-3746. Twenty-four Crl:CD® BR females/group were dosed with Carbofuran technical, 99.1% purity, at 0, 20, 75, or 300 ppm from gestation day 6 to lactation day 10 in a FIFRA-style developmental neurotoxicity study. NOEL = 20 ppm (1.70 to 1.73 mg/kg/day). Higher doses produced sharp reductions in maternal food consumption and body weight (particularly gestation days 6-10), dose-related reductions in pup survival during lactation days 0-4, substantial dose-related reductions in pup body weight gain (persisting in 75 to 300 ppm male pups through day 60), and delays in pup developmental landmarks such as vaginal patency and preputial separation. Several developmental parameters were affected in young pups (up to day 30 measurements) but did not persist to the day 60 measurements. These included brain weight decrements and auditory startle parameters (maximum response and average response). The 300 ppm group lost 13 out of 23 liveborn litters by lactation day 4, thus demonstrating high toxicity. In the water maze test beginning on day 24, learning acquisition was slowed in male pups and often unsuccessful in female pups. Short and long-term memory performance was slightly reduced in 300 ppm males. Learning and memory performance was unaffected at any dose by day 60. There were no neuropathological effects at necropsies (day 11 or day 60) at any dose. Thus doses high enough to elicit neonatal death, marked growth retardation, and developmental delays did not cause treatment-specific or persistent neurological effects. Aldous, 2/10/00.

METABOLISM, MAMMALIAN

There are no metabolism studies on file which were performed according to U. S. EPA guidelines. The best available single volume of miscellaneous metabolism studies is 254-143. Carbofuran is easily oxidized by mammals at the benzylic carbon of the furan group, yielding the 3-hydroxy-furadan. This product can either be conjugated or further oxidized to the corresponding ketone. The N-methycarbamate moiety can also be hydrolytically cleaved to yield 7-hydroxy derivatives (Record No. 097026). Generally, conjugates (sulfate and glucuronide) of the hydrolytic products

predominate in rat urine (accounting for 40 to 70% of dose), whereas 3-hydroxycarbofuran predominates in rat bile. The latter comprised 45% of an oral dose (Record No. 097025). The latter record noted that only about 3% of an oral dose was excreted in feces, hence absorption was efficient. Thus, most objectives sought in an EPA-guideline protocol were obtained in one or both of these published studies. Record Nos. 097020 through 097024, also metabolism studies, did not appear to provide substantial additional information about disposition of oral doses in mammals. No worksheets. Aldous, 1/24/00.

254-012 046593, also 254-009 046821 Exact duplicates of 254-143 097026, above.

RECORDS INDEXED, BUT NOT RELEVANT FOR SUMMARY OF TOXICOLOGY DATA

For exposure/risk assessment data: (158594) Chronic and acute dietary exposure analyses and risk assessment for carbofuran residues in foods and drinking water (145p.) Source lab: unidentified source/source not identified in study or cover documents. Study date: 11/97. Document numbers: 254-161